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The Effects of Long-Term Self-Dosing of Cannabidiol on Drowsiness, Testosterone Levels, and Liver Function

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Abstract

Introduction: Previous research indicated that cannabidiol (CBD) may result in low levels of male total testosterone (TT), elevations in liver tests (LTs), and daytime drowsiness (DD). We investigated the prevalences of TT and LT in a large adult sample self-administering CBD and determined the effect self-dosing of CBD has on the severity of DD. ***Methods:*** Adult participants (18–75 years of age) who self-dose CBD orally for a minimum of 30 days were recruited for this decentralized observational study from companies that offer CBD products. Participants were sent their usual CBD regimen. A clinical study platform was used on a phone app to obtain consent and collect study data. Data included demographic information, reasons for self-dosing, dosage, current medications and dosage, medical history, adverse effects, effects on DD, and efficacy. After 30 days, LT and TT were obtained and follow-up LT was offered to participants who demonstrated elevated values of alanine transaminase (ALT). ***Results:*** A total of 28,121 individuals were contacted, 1,475 met the criteria and were enrolled, and 1,061 (female: 65.2%, male: 34.8%) completed the study. Most of the participants used full-spectrum CBD oil or CBD isolate with the mean ± SD daily dose of CBD for all users of 55.4 ± 37.8 mg. CBD use was associated with a significant decrease in DD and a decrease in the prevalence of low TT in males >40 years of age. The prevalences of elevations in ALT and aspartate aminotransferase were not significantly different from those of the general adult population, and the prevalences of elevated levels of alkaline phosphatase and bilirubin were less than those of a healthy adult population. There was no relationship between LT and CBD dose. ***Conclusions:*** In this large-sample study, self-dosing CBD was not associated with an increased prevalence of elevation of LT or low levels of TT in men. Furthermore, CBD administration decreased DD and was associated with a lower prevalence of low testosterone levels in older men as compared to age-adjusted population norms.

Introduction

Self-administration of cannabidiol (CBD) is increasing rapidly [1, 2]. A recent systematic review indicated that CBD is well tolerated and has a wide range of potential positive effects on a myriad of conditions [3]. The US Food and Drug Administration has expressed concerns

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about the safety of CBD in adults, specifically in regard to its effect on liver tests (LTs), daytime drowsiness (DD), and testosterone levels in men [4].

High doses of CBD have been associated with elevated LFT and somnolence in children with epilepsy, and these effects were strongly related to the dose of CBD [5]. Similar findings have been found in adults where consuming high doses of CBD (1,500 mg/day) is associated with elevated LFT and adverse side effects, while lesser doses of CBD (20–1,000 mg/day) resulted in no increase in LT or adverse side effects [5–7]. In all of these studies, the dose of CBD was controlled by the investigators and/or the patient population included only individuals with a specific disease. However, this is not representative of the most common use of CBD in the USA, i.e., self-administration and self-dosing of CBD.

Elevated LT in the adult population ranges from 10 to 20% with the prevalence of elevated alanine aminotransferase (ALT) being 8.9% and the prevalence of elevated aspartate aminotransferase (AST) being 4.9% [8, 9]. Because intermittent elevations of LT are common in normal individuals, it is paramount to assess liver function using multiple LTs including ALT, AST, alkaline phosphatase (ALP), and total bilirubin (TB) [4]. In addition, most recommend that when evaluating ALT and AST levels, a cut-off of >3 times the upper limit of normal be used as an indicator of possible liver disease and that values be repeated and evaluated in context with the other LT [5–9].

In a previous report of 839 people self-dosing CBD, the prevalences of elevated ALT and AST were not different from the general population and 91% of those who had elevated ALT levels had normal or minimally elevated ALT levels (<2x ULN) on a later LT [10]. The current study contains the data from those individuals and adds the data from another 222 individuals to examine the impact of long-term self-dosing of CBD on DD in all individuals and testosterone levels in males.

Materials and Methods

This study was conducted in accordance with international ethical standards on human experimentation with institutional review board approval and supervision provided by Adverra. This was a decentralized, real-world study, with all interaction between participants and study personnel occurring through a phone app, a secure 21CFR Part 11 decentralized clinical study platform developed by Validcare, LLC. Adults living in the USA aged 18–75 years were recruited via social media to a recruiting page on the phone app. After signing consent, participants were included if they had been taking CBD for the last 30 days or more and excluded if they had been using marijuana in the last 30 days or if they met any of the following criteria: liver function impairment, liver disease, allergies to CBD, or taking any of these medications which are known to cause elevated LT: valproate, vitamin A, clobazam, cyclosporine, phenytoin, fluvoxamine, isoniazid, ritonavir, clarithromycin, diltiazem, erythromycin, grapefruit juice, itraconazole, ketoconazole, nefazodone, ritonavir, telithromycin, or verapamil. After choosing which manufacturer and which CBD regimen (full spectrum: containing all the cannabinoids, flavonoids, and terpenes commonly found in hemp oil; broad spectrum: containing CBD and some or all of the compounds found in hemp oil but not THC; or CBD isolate: containing only CBD) they wanted to use for the study, their choices were mailed to them through a third party. Using the app, the following initial data were collected: weight, height, age, sex, medical history, reasons for taking CBD, present dosage, form of CBD, composition of CBD, current prescribed (Rx) and over-the-counter medications, alcoholic drinks per day, number and type of medical conditions/diseases, number and type of other therapies, number of days, and type of cannabinoid treatments they had been using for the last 30 days. Participants were asked weekly for changes in any of these data. Daily journaling provided additional information on CBD dosage, DD, and adverse effects. DD was quantified using the Stanford Sleepiness Scale (SSS) (Table 1).

A total of 30 days of daily journal data were collected, after which blood draws were taken locally and sent to a national laboratory. Serum was analyzed for the LT: ALT, AST, TB, and ALP for all individuals, and in men, total testosterone (TT) levels were obtained. Low testosterone levels were defined as <300 ng/mL [11, 12]. Because two different national laboratories were used and their upper limits of normal for ALT were different, ALT values were adjusted to the percentile of the upper limit of normal for their laboratory to allow accurate comparisons of the severity of any elevations of ALT between laboratories. Participants who demonstrated elevated ALT were offered follow-up LT. For those individuals who choose to obtain follow-up LT, medical history, medication history, and cannabinoid use history data were obtained during the time period between the LT. If participants did not want to accept the follow-up LT, they were asked to provide the LT information if it had been obtained from their local medical professional. Data were analyzed with standard and paired *t* tests, repeated measures, stepwise linear regression, Z tests, and χ^2 tests, as appropriate.

Results

A total of 1,475 participants were enrolled in the app and 1,061 completed the study. Participants resided in 49 different states. The main reason for dropout (382/414, 92.3%) was not obtaining a blood test for fear of contracting COVID by being in public places. There were 692 women (65.2%) and 369 men (34.8%) with an age range of 19–75 years and a mean age of 46.6 ± 12.9 years. There was no age difference between women and men (46.9 ± 12.9 and 46.2 ± 13.0, respectively). Most of the participants had been using CBD for over 1 year with 1–3 months being the second most common length of use, as shown in Figure 1. Tinctures were the most commonly ingested form of CBD, with most tinctures being full-spectrum products (Table 2).

Table 1. Stanford Sleepiness Scale

Stanford Sleepiness Scale	
1	Feeling active, vital, alert, or wide awake
2	Functioning at high levels, but not at peak: able to concentrate
3	Relaxed, awake but not fully alert: responsive
4	A little foggy
5	Foggy, beginning to lose track: having difficulty staying awake
6	Sleepy, woozy, fighting sleep: prefer to lie down
7	Cannot stay awake, sleep onset appears imminent

One brand had an oral, full-spectrum CBD product formulated using nanotechnology. Statistical analysis of CBD dosing found that participants who used this product consumed an average daily dose that was significantly lower than all other forms of CBD. Due to this, in all comparisons of daily dose with other parameters, the data from the 106 nano-CBD users were excluded and only the data from the 945 non-nano-CBD users were used.

The full-spectrum products were the most commonly ingested CBD composition (Table 3) The mean daily dose of full-spectrum CBD was significantly lower than that of CBD isolate and broad-spectrum CBD ($p = 0.013$ and $p < 0.001$, respectively). The statistical mode for each composition of CBD is less than the mean, and the top of the range is several times that of the mean for each group. The ANOVA tests revealed that the composition and form of CBD were independent predictors of the daily dose of CBD ($p < 0.001$ and $p = 0.004$, respectively).

Using repeated measures, for all levels of baseline SSS, the baseline SSS was significantly different from the SSS for each week for weeks 1 through 4 but there was no difference between weeks 1 through 4. Therefore, the average SSS from weeks 1 through 4 was compared with the baseline SSS using paired *t* tests (Table 4). The average SSS increased significantly for those with baseline SSS ≤2 and decreased significantly for those with baseline SSS ≥3. CBD seemed to be normalizing the SSS around the 2–3 level as those with baseline SSS ≥3 had significantly more reduction in their SSS than those with baseline SSS ≤2 had of augmentation ($p < 0.001$) (Table 4). Only 4 of 851 individuals (0.5%) progressed from not having DD (SSS <5) to experiencing DD (SSS ≥5), while 43 of 49 (87.8) who initially had DD progressed to not having DD.

TT levels were available in 358 of the 369 males and 78 (21.8%) had a low level (<300 ng/mL). TT was negatively correlated with weight and BMI but not with age. The prevalence of low TT was compared with population norms (Table 5). The prevalence of low TT does not increase with age in this study as it does in the normal population [11]. This decrease in prevalence is not due to exogenously administered testosterone, as only 4 individuals took testosterone supplementation (2 oral and 2 topical), 3 of whom had diabetes and the other had known primary testosterone deficiency. TT was negatively correlated with weight and BMI but not with age, while the daily dose of CBD per kg of body weight was positively correlated with TT ($r = 0.16$, $p = 0.004$) and negatively with low TT ($r = 0.11$, $p = 0.036$). Multiple linear regression found that after controlling for weight, the daily dose of CBD was partially correlated with TT (CC 0.095, $p = 0.072$).

Because weight and BMI are risk factors for type 2 diabetes, which is a risk factor for low testosterone, the prevalence of type 2 diabetes was examined by querying the medical history. Individuals reporting type 2 diabetes were included and individuals taking oral medications used to treat type 2 diabetes were also included in the analysis. The prevalences of type 2 diabetes in the whole study group (men and women) and in men only by age group were compared with the norms of the general population (Table 6). In those less than 45 years of age, the prevalence of type 2 diabetes, in general and in men, was the same as that of the general population; however, in those over 45 years of age, the prevalence of type 2 diabetes was significantly lower than that of the general population in the whole study group and in men [12].

The prevalence of elevated ALT was 9.1% and the prevalence of AST was 4.1%, both of which are not significantly different from the reported prevalences in the general adult US population: 8.9% for ALT and 4.9% for AST ($p = 0.819$ and 0.227, respectively) [7]. The prevalence of TB and ALP was 1.7%, which is not statistically different compared to the prevalence of the normal population of 2.5% ($p = 0.095$). Of the 97 participants with elevated ALT, 73 were <2x ULN, 14 were between 2x and 3x ULN, and 4 individuals were >3x ULN. In those with ALT >3x ULN, all 4 had elevated AST levels. The percentage with elevated AST levels decreased to 85.7% for those with ALT >2x ULN and was 32.0% for participants when ALT >1x ULN. Only one individual had a TB level greater than the ULN of ≤1.2 mg/dL. This individual's TB level was 1.3 with an elevated ALT of <2x ULN and both AST and ALP were normal. Only 4

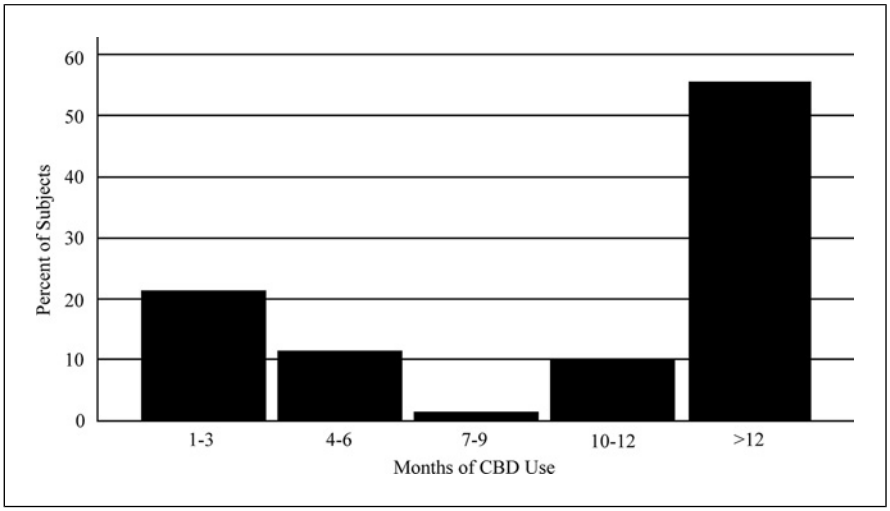

Fig. 1. Percent of subjects per each period of use (in months).

Table 2. Composition and daily dose for the different forms of CBD

Form of CBD	*N*	%	Composition			CBD dosage, mg/day		
			FS[a]	BS[b]	CBD-I[c]	mean	SD	range
Tincture	566	53.3	331	109	126	54.7	36.1	8–245
Capsule/pill	221	20.8	88	36	97	60.7#	46.8	24–390
Edible	154	14.5	0	16	138	50.0#	27.5	23–170
Nano[d]	106	10.0	106	0	0	7.6*	3.0	2.5–25.5
Additive	14	1.3	0	14	0	66.5	33.4	50–140

SD, standard deviation. [a]FS, full spectrum. [b]BS, broad spectrum. [c]CBD-I, CBD isolate. [d]Nanotechnology-treated CBD. *Different than all others ($p < 0.001$). #Different than each other ($p = 0.016$).

Table 3. Daily dose for different compositions of all CBD products except nano-CBD

Composition of CBD	*N*	%	CBD dosage (mg/day)			
			mean	SD	range	median
Overall	955	100.0	55.4	37.8	8–390	42.9
Full spectrum	419	43.9	48.8*#	34.4	8–210	39.0
CBD isolate	361	37.8	63.6*	42.6	15–390	50.0
Broad spectrum	175	18.3	54.0#	31.3	16.5–185	50.0

SD, standard deviation. *$p = 0.013$. #$p < 0.001$.

individuals had minor elevations in ALP and all had ALT levels <2x ULN.

Correlation analyses demonstrated that age, BMI, and gender were highly correlated with the ALT percentile level. However, a multiple regression analysis found that only BMI ($p < 0.001$) and age ($p < 0.05$) predicted elevated ALT. There were no statistical differences in the mean daily dose of individuals with elevated AST (mg/day) and for those with normal AST (55.4 ± 39.2 vs. 50.1 ± 38.5 mg/day; $p = 0.200$). There were no significant relationships between any of the other variables and ALT levels. The analyses indicated that there was no significant difference in elevated incidence of LT between CBD brands (Table 7) or between the compositions or forms of CBD.

The percentage of individuals with chronic medical conditions was 66.4% of the total subjects, with 38.2% having multiple chronic medical conditions, both significantly higher than those found in the general population (51.8% and 27.2%,

Table 4. Stanford Sleepiness Scores (SSS): baseline compared to average of weeks 1–4

Baseline	Average weeks 1–4	SD	#	*p* value	SSS change
1	1.62	0.69	243	<0.001	+0.62
2	2.16	0.77	350	<0.001	+0.16
3	2.59	0.96	141	<0.001	−0.41
4	2.98	1.09	117	<0.001	−1.02
5	3.60	1.12	43	<0.001	−1.4
6	3.52	1.57	16	<0.001	−2.48
7	3.19	2.42	4	0.051	−3.81

SD, standard deviation.

Table 5. Prevalence of low TT levels compared to population norms by age group

Age	#	Our data		Population norms	*p* value
		#	%		
<40	132	29	22	23%	0.878
40–59	158	35	22	36%	0.001
≥60	68	14	21	35%	0.019

Table 7. Prevalence of elevated ALT for each company

Company number*	#Subjects	Elevated ALT	
		#	%
100	43	8	18.6%
300	55	8	14.5%
400	106	9	8.5%
500	84	8	9.5%
600	62	4	6.5%
700	145	17	11.7%
800	71	5	7.0%
900	70	6	8.6%
1000	14	2	14.3%
1100	53	4	7.5%
1200	54	7	13.0%
1300	82	7	8.5%
1400	77	9	11.7%
1500	58	7	12.1%
1600	36	1	2.8%
1700	30	1	3.3%
1800	21	3	14.3%
Total	1,061	106	100.0%

*Company number is used for Company Name.

Table 6. Prevalence of type 2 diabetes by age and in males only as compared to population norms

Age	Prevalence (females and males)			Prevalence (males only)		
	study	population norms	*p* value	study	population norms	*p* value
<45	1.7%	2.1%	0.517	3.2%	2.9%	0.806
45–64	3.4%	11.1%	<0.001	3.4%	12.1%	<0.001
>65	6.1%	18.2%	<0.001	8.6%	19.8%	0.0418

respectively) [13]. In the individuals with normal ALT values, 66.9% had chronic medical conditions with a mean of 2.8 ± 2.4 conditions per subject, while 60.8% of those with elevated ALT values had chronic medical conditions with a mean of 3.0 ± 2.9. Similarly, subjects taking prescription drugs with normal ALT levels took 2.4 ± 2.6 drugs and those with elevated ALT levels reported using 2.7 ± 2.1 drugs. There were no significant differences for any of these variables.

Of the 97 individuals with elevated LT, 43 agreed to the follow-up LT performed by our laboratories ($N = 36$) or by their healthcare professional [7]. The remaining participants refused a follow-up LT or did not appear for the test. Of the participants who had follow-up LT data, 26 (60.5%) had normal ALT, which is significantly higher than the 31% who return to normal after having elevated ALT as found in the general population ($p = 0.007$) [14]. Of the remaining, 10 stayed at the same level, 6 had an increase in level, and 1 had a decrease in level.

Five individuals had a repeat ALT level >3x ULN, all of whom had an elevated AST, none had any elevation in bilirubin, and one had an elevated ALP, which had been elevated in the initial laboratory draw. One individual had a level 3x ULN for both tests during this study, but this individual had persistent elevated ALT and AST prior to the study. One individual had an initial level of 2x ULN. This person was an alcoholic who, while taking CBD, decreased her alcohol consumption but increased back to her original alcohol consumption prior to FU LT because she was no longer taking CBD. Three individuals had an initial level of 1x ULN. One was a diabetic who had a third set of LTs which were normal even though she continued to take CBD and was taking lisinopril, meloxicam, and glimepiride, known drugs associated with intermittent elevated LT. One had a history of transient elevations of LT in the past and a third set of LTs that were normal. The last person had been taking CBD for years and, just before

starting the study, had normal LT before starting red yeast rice (a known liver toxin [15, 16]) for elevated cholesterol. After the second LT, she saw her doctor and had an MRI that showed liver inflammation. She stopped red yeast rice, continued to take CBD, and her LT returned to normal.

The analyses indicate that there was no association between the continuation of CBD, daily dose, and ALT levels or the change in the severity of the elevation of ALT. Of the 43 participants with elevated levels, 95.3% (n = 41) of them experienced a return to normal or only minimally elevated (<2x ULN) levels. As previously discussed, participants with significantly elevated ALT (>3x ULN) indicated explanations for the elevation outside of CBD ingestion.

In the current study, 33 participants (2.2%) reported the presence of an adverse reaction (AE). Of these 2 were considered probably related to CBD ingestion (one subject with atrial fibrillation who discontinued the study and another constipation and psychoactive effects occurring simultaneously that resolved); 10 were considered possibly related and all spontaneously resolved (muscle spasm, swelling, hives, coughing, anxiety [2], joint inflammation [2], and atrial fibrillation); 3 were considered unlikely related and all resolved spontaneously (hypertension, constipation, unpleasant feeling in chest); and 18 were considered unrelated (sore throat, cough, UTI, abdominal pain, neck pain all which spontaneously resolved); yeast infection that was treated and resolved; degenerative disc, TMJ flair, osteoarthritis, cholelithiasis, back pain [2], knee pain, and anemia all which were present prior to the study and all subjects finished the study; COVID [2], pneumonia, and shingles all of which withdrew from the study).

Discussion

The ALT data analysis in this study is similar to other studies that demonstrate that the level of ALT is affected by BMI, age, and gender, suggesting that the current sample is representative of the general adult population [17, 18]. These data indicate that the occurrence of elevated ALT and/or AST was not different from those of the adult population of the USA and that elevated LT returned to normal even when CBD use is sustained [7, 8]. In the very small number of participants with persistent severely elevated or worsening severity of elevated ALT, the cause can be explained by variables extraneous to CBD ingestion, including but not limited to chronic conditions and associated medications. In this large-sample study of participants who self-dose CBD, the prevalence of elevated ALT was 9.1%, which is not significantly different from the prevalence reported in the general adult population of the USA (8.9%) [7]. Furthermore, no participants demonstrated liver disease in the current study, and the prevalences of ALP and TB in this sample were lower than the prevalences in the normal healthy adult population. These data suggest that CBD may help prevent liver disease in some individuals, a finding found in animal and in vitro studies [19, 20].

In the current study, a large number of participants reported using various medications, including those known to elevate LT. In related studies, this has been a common theme when CBD use and LT elevations are investigated together, yet the daily dose in clinical trials (10–20 mg/kg) is a significant mediator of this relationship [4, 5]. In our study, the average daily dose was 0.65 ± 0.57 mg/kg/day, which is an order of magnitude lower and comparable to the daily dose typically consumed by a self-dosing CBD user. This paradoxical effect on drug-induced liver damage with different dose levels of CBD is not new [21]. Although it may be possible that lower doses of CBD can cause transient elevations in LT, our data indicate that any significant elevations are associated with demographic, physical, and medical conditions.

The literature is contradictory with respect to the effect of CBD on sleep in both human and animal studies, as some do not find an effect [22–24], some show significant improvements [22–31], and some show detrimental effects [22, 27, 32–34]. The data from this study suggest that these differences may be due to the underlying quality of sleep of individuals and the severity of DD. In humans with anxiety, daily low-dose CBD (25–50 mg/day) improves sleep; in normal individuals, a moderate single dose (300 mg) has no effect on sleep, but chronic administration of a moderate to high dose (600 mg/day) causes drowsiness in 20% [29, 32]. In one study, high-dose CBD use in individuals with epilepsy (10–20 mg/kg) causes drowsiness in 30% of individuals, but a different study found that it improves sleep and reduces DD [22, 27]. In rats, CBD improves sleep and decreases drowsiness during times of wakefulness [30, 31, 34].

As in other studies, the prevalence of low testosterone was negatively correlated with weight and BMI, but it did not increase with age as is typical in other studies [11, 35, 36] causing the prevalence of low testosterone in older individuals taking CBD to be much lower than compared to the general population. In rodent studies, CBD has been shown to cause low testosterone levels and adversely affect testicular morphology and endocrine function [37]. In this study, a cofactor associated with low testosterone, type 2 diabetes had a prevalence much lower than expected (study = 3.2% vs. population = 9.1%) [38]. The prevalence of type 2 diabetes also increases with age, which occurred in this study;

however, the magnitude of the increase was a fraction of what would normally be expected. In animal models of diabetes, CBD and other cannabinoids have been shown to prevent the development of diabetes when administered prophylactically and/or to improve diabetes and diabetic complications when administered as therapy to animals with established diabetes [39–44]. It cannot be definitively determined in this study whether the low prevalences of testosterone deficiency and type 2 diabetes are related due to the low number of both entities. However, it is unlikely that these low prevalences were due to a healthier population than normal, given that the number of medical conditions per individual is more than that found in the general population [13]. This discovery needs to be explored in more detail.

In this large-sample study of individuals self-dosing CBD, CBD use decreased DD for most participants, decreased the prevalence of diabetes in older individuals, decreased the prevalence of low testosterone in older males, and did not increase the prevalence of liver disease. Significant elevations in LF were associated with medical conditions or medications known to cause liver disease and were not related to the consumption of CBD.

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Statement of Ethics

This study was carried out in accordance with the guidelines on human experimentation in accordance with the Declaration of Helsinki of the World Medical Association with the approval and supervision of the Institutional Review Board provided by Advarra, 00043515. Signed informed consent was obtained from all participants before beginning the study.

Conflict of Interest Statement

Robert Kaufmann has served as a consultant for Shaman Botanicals, LLC, and Validcare, LLC, and as a speaker for Shaman Botanicals, LLC. Amber Harris Bozer, Amanda Kube, and Keith Aqua have no conflicts of interest to declare.

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Author Contributions

Robert Kaufmann was the study project manager, designed and wrote the protocol, and is the primary author of the manuscript. Amber Harris Bozer assisted with the analysis, interpretation, writing, and final approval of the data. Amanda Rose Kube Jotte performed the statistical calculations and assisted with analysis, writing, and final approval. Keith Aqua was the primary investigator for the study that directed data acquisition, intellectual content review, and final approval.

Data Availability Statement

Due to legal reasons, the dataset is not available for public viewing but can be made available, on request, for confirmation of statistics if requested by an accredited peer-reviewed committee or government agency. Further inquiries can be directed to the corresponding author.

References

1 Wellbeing BM. 14% of Americans say they use CBD products. Washington DC: Gallup; 2019 Aug 7. [cited 2022 May 7]. Available from: https://news.gallup.com/poll/263147/americans-say-cbd-products.aspx.

2 Single Care team/wellness. The 2020 CBD survey. The Checkup; 2020 Apr. [cited 2022 May 8]. Available from: https://www.singlecare.com/blog/cbd-survey/.

3 Millar SA, Stone NL, Bellman ZD, Yates AS, England TJ, O'Sullivan SE. A systematic review of cannabidiol dosing in clinical populations. Br J Clin Pharmacol. 2019; 85(9):1888–900.

4 U.S. Food and Drug Administration. What you need to know (and what we're working to find out) about products containing cannabis or cannabis-derived compounds, including CBD; 2020. [cited 2022 Nov 24]. Available from: https://www.fda.gov/consumers/consumer-updates/what-you-need-know-and-what-were-working-find-out-about-products-containing-cannabis-or-cannabis.
5 Chesney E, Oliver D, Green A, Sovi S, Wilson J, Englund A, et al. Adverse effects of cannabidiol: a systematic review and meta-analysis of randomized clinical trials. Neuropsychopharmacology. 2020;45(11):1799–806.
6 Watkins PB, Church RJ, Li J, Knappertz V. Cannabidiol and abnormal liver chemistries in healthy adults: results of a phase I clinical trial. Clin Pharmacol Ther. 2021;109(5):1224–31.
7 Morrison G, Crockett J, Blakey G, Sommerville K. A phase 1, open-label, pharmacokinetic trial to investigate possible drug-drug interactions between clobazam, stiripentol, or valproate and cannabidiol in healthy subjects. Clin Pharmacol Drug Dev. 2019;8(8):1009–31.
8 Radcke S, Dillon JF, Murray AL. A systematic review of the prevalence of mildly abnormal liver function tests and associated health outcomes. Eur J Gastroenterol Hepatol. 2015;27(1):1–7.
9 Ioannou GN, Boyko EJ, Lee SP. The prevalence and predictors of elevated serum aminotransferase activity in the United States in 1999–2002. Am J Gastroenterol. 2006;101(1):76–82.
10 Kaufmann R, Aqua K, Lombardo J, Lee M. Observed impact of long-term consumption of oral cannabidiol on liver function in healthy adults. Cannabis Cannabinoid Res. 2023;8(1):148–54.
11 Peterson MD, Belakovskiy A, McGrath R, Yarrow JF. Testosterone deficiency, weakness, and multimorbidity in men. Sci Rep. 2018;8(1):5897.
12 Masterson JM, Soodana-Prakash N, Patel AS, Kargi AY, Ramasamy R. Elevated body mass index is associated with secondary hypogonadism among men presenting to a tertiary academic medical center. World J Mens Health. 2019;37(1):93–8.
13 Boersma P, Black LI, Ward BW. Prevalence of multiple chronic conditions among US adults. Prev Chronic Dis. 2018;17:E106.
14. Lazo M, Selvin E, Clark JM. Brief communication: clinical implications of short-term variability in liver function test results. Ann Intern Med. 2009 Apr 72008;148(5):348–52.
15 Younes M, Aggett P, Aguilar F, Crebelli R, Dusemund B, et al. EFSA Panel on Food Additives and Nutrient Sources added to Food ANS. Scientific opinion on the safety of monacolins in red yeast rice. EFSA J. 2018;16(8):e05368.
16 Red yeast rice: muscle and liver disorders. Prescrire Int. 2015;24(161):156.
17 Kariv R, Leshno M, Beth-Or A, Strul H, Blendis L, Kokia E, et al. Re-evaluation of serum alanine aminotransferase upper normal limit and its modulating factors in a large-scale population study. Liver Int. 2006;26(4):445–50.
18 Piton A, Poynard T, Imbert-Bismut F, Khalil L, Delattre J, Pelissier E, et al. Factors associated with serum alanine transaminase activity in healthy subjects: consequences for the definition of normal values, for selection of blood donors, and for patients with chronic hepatitis C. MULTIVIRC Group. Hepatology. 1998;27(5):1213–9.
19 Berk K, Bzdega W, Konstantynowicz-Nowicka K, Charytoniuk T, Zywno H, Chabowski A. Phytocannabinoids-A green approach toward non-alcoholic fatty liver disease treatment. J Clin Med. 2021;10(3):393.
20 Wang Y, Mukhopadhyay P, Cao Z, Wang H, Feng D, Haskó G, et al. Cannabidiol attenuates alcohol-induced liver steatosis, metabolic dysregulation, inflammation and neutrophil-mediated injury. Sci Rep. 2017;7(1):12064.
21 Ewing LE, McGill MR, Yee EU, Quick CM, Skinner CM, Kennon-McGill S, et al. Paradoxical patterns of sinusoidal obstruction syndrome-like liver injury in aged female CD-1 mice triggered by cannabidiol-rich cannabis extract and acetaminophen co-administration. Molecules. 2019;24(12):2256.
22 Kolla BP, Hayes L, Cox C, Eatwell L, Deyo-Svendsen M, Mansukhani MP. The effects of cannabinoids on sleep. J Prim Care Community Health. 2022;13:21501319221081277.
23 Kaul M, Zee PC, Sahni AS. Effects of cannabinoids on sleep and their therapeutic potential for sleep disorders. Neurotherapeutics. 2021;18(1):217–27.
24 Linares IMP, Guimaraes FS, Eckeli A, Crippa ACS, Zuardi AW, Souza JDS, et al. No acute effects of cannabidiol on the sleep-wake cycle of healthy subjects: a randomized, double-blind, placebo-controlled, crossover study. Front Pharmacol. 2018;9:315.
25 Anderson CL, Evans V, Gorham L, Liu Z, Johnson CR, Carney PR. Seizure frequency, quality of life, behavior, cognition, and sleep in pediatric patients enrolled in a prospective, open-label clinical study with cannabidiol. Epilepsy Behav. 2021;124:108325.
26 Chagas MH, Crippa JA, Zuardi AW, Hallak JE, Machado-de-Sousa JP, Hirotsu C, et al. Acute systemic administration of cannabidiol on sleep-wake cycle in rats. J Psychopharmacol. 2013;27:312–6.
27 Sznitman SR, Vulfsons S, Meiri D, Weinstein G. Medical cannabis and insomnia in older adults with chronic pain: a cross-sectional study. BMJ Support Palliat Care. 2020;10(4):415–20.
28 Murillo-Rodríguez E, Sarro-Ramírez A, Sánchez D, Mijangos-Moreno S, Tejeda-Padrón A, Poot-Aké A, et al. Potential effects of cannabidiol as a wake-promoting agent. Curr Neuropharmacol. 2014;12(3):269–72.
29 Murillo-Rodríguez E, Machado S, Imperatori C, Yamamoto T, Budde H. Natural cannabinoids as templates for sleep disturbances treatments. Adv Exp Med Biol. 2021;1297:133–41.
30 Shannon S, Lewis N, Lee H, Hughes S. Cannabidiol in anxiety and sleep: a large case series. Perm J. 2019;23:18–041.
31 Murillo-Rodríguez E, Millán-Aldaco D, Cicconcelli D, Giorgetti V, Arankowsky-Sandoval G, Alcaraz-Silva J, et al. Sleep-wake cycle disturbances and NeuN-altered expression in adult rats after cannabidiol treatments during adolescence. Psychopharmacology. 2021;238(6):1437–47.
32 Hsiao YT, Yi PL, Li CL, Chang FC. Effect of cannabidiol on sleep disruption induced by the repeated combination tests consisting of open field and elevated plus-maze in rats. Neuropharmacology. 2012;62(1):373–84.
33 Laux LC, Bebin EM, Checketts D, Chez M, Flamini R, Marsh ED, et al. Long-term safety and efficacy of cannabidiol in children and adults with treatment resistant Lennox-Gastaut syndrome or Dravet syndrome: expanded access program results. Epilepsy Res. 2019;154:13–20.
34 Boggs DL, Surti T, Gupta A, Gupta S, Niciu M, Pittman B, et al. The effects of cannabidiol (CBD) on cognition and symptoms in outpatients with chronic schizophrenia a randomized placebo controlled trial. Psychopharmacology (Berl). 2018;235(7):1923–32.
35 Araujo AB, O'Donnell AB, Brambilla DJ, Simpson WB, Longcope C, Matsumoto AM, et al. Prevalence and incidence of androgen deficiency in middle-aged and older men: estimates from the Massachusetts Male Aging Study. J Clin Endocrinol Metab. 2004;89(12):5920–6.
36 Del Giudice F, Kasman AM, Ferro M, Sciarra A, De Berardinis E, Belladelli F, et al. Clinical correlation among male infertility and overall male health: a systematic review of the literature. Investig Clin Urol. 2020;61(4):355–71.
37 Carvalho RK, Andersen ML, Mazaro-Costa R. The effects of cannabidiol on male reproductive system: a literature review. J Appl Toxicol. 2020;40(1):132–50.
38 Xu G, Liu B, Sun Y, Du Y, Snetselaar LG, Hu FB, et al. Prevalence of diagnosed type 1 and type 2 diabetes among US adults in 2016 and 2017: population based study. BMJ. 2018;362:k1497.
39 Weiss L, Zeira M, Reich S, Slavin S, Raz I, Mechoulam R, et al. Cannabidiol arrests onset of autoimmune diabetes in NOD mice. Neuropharmacology. 2008;54(1):244–9.

40 Weiss L, Zeira M, Reich S, Har-Noy M, Mechoulam R, Slavin S, et al. Cannabidiol lowers incidence of diabetes in non-obese diabetic mice. Autoimmunity. 2006 Mar; 39(2):143–51.
41 Stanley CP, Wheal AJ, Randall MD, O'Sullivan SE. Cannabinoids alter endothelial function in the Zucker rat model of type 2 diabetes. Eur J Pharmacol. 2013;720(1–3): 376–82.
42 Toth CC, Jedrzejewski NM, Ellis CL, Frey WH 2nd. Cannabinoid-mediated modulation of neuropathic pain and microglial accumulation in a model of murine type I diabetic peripheral neuropathic pain. Mol Pain. 2010;6:16.
43 González-Mariscal I, Pozo-Morales M, Romero-Zerbo SY, Espinosa-Jimenez V, Escamilla-Sánchez A, Sánchez-Salido L, et al. Abnormal cannabidiol ameliorates inflammation preserving pancreatic beta cells in mouse models of experimental type 1 diabetes and beta cell damage. Biomed Pharmacother. 2022;145:112361.
44 González-Mariscal I, Carmona-Hidalgo B, Winkler M, Unciti-Broceta JD, Escamilla A, Gómez-Cañas M, et al. (+)-trans-Cannabidiol-2-hydroxy pentyl is a dual CB_1R antagonist/CB_2R agonist that prevents diabetic nephropathy in mice. Pharmacol Res. 2021;169: 105492.